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Editor's comment: Daytime somnolence is one of the most common non-motor complaints encountered in Parkinson's disease (PD) patients. In its most severe form it can become a major source of disability and a significant contributor to a very poor quality of life. As such, it is extremely important for clinicians to understand its origins and associations in persons suffering from PD. In this article, Goldman and colleagues, using well-validated measures of sleepiness and cognition, determine that cognitive decline in persons with PD is clearly associated with excessive daytime sleepiness, whereas, contrary to what you might expect, it has no bearing on the quality of nocturnal sleep in these patients. In our quest to lighten the burden of Parkinson's disease, the authors of this study bring us closer to a full understanding of one of this disorder's most perplexing and disabling components.

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Dissociations among daytime sleepiness, nighttime sleep, and cognitive status in Parkinson's disease

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ABSTRACT

Background: Daytime and nighttime sleep disturbances and cognitive impairment occur frequently in Parkinson's disease (PD), but little is known about the interdependence of these non-motor complications. Thus, we examined the relationships among excessive daytime sleepiness, nighttime sleep quality and cognitive impairment in PD, including severity and specific cognitive deficits.
Methods: Ninety-three PD patients underwent clinical and neuropsychological evaluations including the Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI). Patients were classified as having normal cognition (PD-NC), mild cognitive impairment (PD-MCI), or dementia (PDD) using recently proposed Movement Disorder Society PD-MCI and PDD criteria. Relationships between the sleep and cognitive measures and PD cognitive groups were examined.
Results: The PD cohort included PD-NC ($n = 28$), PD-MCI ($n = 40$), and PDD ($n = 25$) patients. ESS scores, as a measure of daytime sleepiness, were significantly worse ($p = 0.005$) in cognitively impaired PD patients, particularly PDD patients. ESS scores correlated significantly with Mini-Mental State Examination scores and also with cognitive domain scores for attention/working memory, executive function, memory, and visuospatial function. In contrast, PSQI scores, as a measure of nighttime sleep quality, neither differed among cognitive groups nor correlated with any cognitive measures.
Conclusions: Daytime sleepiness in PD, but not nighttime sleep problems, is associated with cognitive impairment in PD, especially in the setting of dementia, and attention/working memory, executive function, memory, and visuospatial deficits. The presence of nighttime sleep problems is pervasive across the PD cognitive spectrum, from normal cognition to dementia, and is not independently associated with cognitive impairment or deficits in cognitive domains.

1. Introduction

Sleep disturbances are common in Parkinson's disease (PD), occurring in over 75% of patients and affecting both daytime and nighttime function [1]. The etiology of daytime and nighttime sleep problems in PD is likely multi-factorial, with contributions from neurochemical and neuropathological changes associated with PD

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as well as other features such as medication effects, mood disorders, and recurrent motor symptoms [2]. Prior studies of daytime and nighttime sleep problems in PD have suggested that excessive daytime sleepiness may be an integral part of PD pathology rather than the result of poor nighttime sleep [3,4]; however, these studies were not designed specifically to examine how daytime and nighttime sleep disturbances relate to cognitive status or types of cognitive deficits in PD. Other studies have suggested an association between excessive daytime sleepiness [5] and rapid eye movement sleep behavior disorder (RBD) [6] with cognitive decline or dementia in PD, but have focused generally on either daytime or nighttime sleep problems individually, rather than their interdependence. Thus, the interdependence of these sleep-wake problems across the cognitive spectrum of PD, from normal cognition to dementia, merits investigation.

These knowledge gaps are particularly important because sleep disturbances in PD may have deleterious consequences on cognitive function, an association that is well recognized in the general population and growing in the PD literature [7,8]. To our knowledge, no studies have examined the relationships among daytime sleepiness, nighttime sleep quality, and cognitive impairment across the full PD cognitive spectrum including patients not only with normal cognition (PD-NC) and dementia (PDD), but also those with mild cognitive impairment (PD-MCI), which recently has been defined by a Movement Disorder Society (MDS) task force [9] and may represent a prodromal state heralding incipient dementia [10–12]. Identified associations between specific features of sleep-wake dysfunction and cognitive problems in PD may signify harbingers of cognitive decline from PD-NC to PD-MCI and to PDD and ultimately, may lead to interventions that could improve both sleep and cognitive symptoms and modify risk factors for cognitive decline. Moreover, studies of sleep-wake problems across a broad range of PD cognitive function may reveal how these sleep disturbances vary not only with cognitive status, but also with deficits in specific cognitive domains.

Accordingly, the overall goal of our study was to investigate the relationships among excessive daytime sleepiness, nighttime sleep quality, and cognitive impairment in PD. Our first aim was to examine self-reported daytime and nighttime sleep disturbances, measured by, respectively, the Epworth Sleepiness Scale (ESS) [13] and Pittsburgh Sleep Quality Index (PSQI) [14] in a PD cohort represented by PD-NC, PD-MCI, and PDD patients. These two scales are easily administered, widely used, and deemed “Recommended” measures by the MDS Sleep Scale Task Force for screening and measuring the severity of sleep problems in PD [15]. Our second aim was to investigate the relationship between sleep disturbances and specific cognitive domains including attention and working memory, executive function, language, memory, and visuospatial function.

2. Methods

2.1. Participants

Ninety-three PD patients were recruited from the Rush University Movement Disorders clinic as part of a prospective study of clinical and neuroimaging markers of PD cognitive impairment. PD patients met United Kingdom PD Society Brain Bank criteria, had a disease duration of at least 4 years at the time of initial study evaluation, and were examined by a movement disorders neurologist (J.G.G.). Exclusionary criteria were: atypical or secondary parkinsonism (e.g., dementia with Lewy bodies, multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, or parkinsonism due to neuroleptic exposure, cerebrovascular disease, or known structural causes); severe or unstable depression; anticholinergic medications (e.g., trihexyphenidyl, benztropine, tricyclic antidepressants); and other medical/neurological causes of cognitive impairment (e.g., seizures, strokes, head trauma, known untreated or unstable primary sleep disorders including obstructive sleep apnea). In patients with dementia, all had motor symptoms for at least one year prior to dementia onset. The study was approved by the Rush University Institutional Review Board in Chicago, IL; all participants gave written informed consent to take part in the study.

2.2. Evaluations

Clinical evaluations included assessments of demographics, disease-related features, and medication use. Sleep measures included the ESS and PSQI, which were administered to each patient to assess, respectively, daytime sleepiness and nighttime sleep quality; for all patients, regardless of cognitive status, responses to the sleep scales were corroborated with input from their informant (e.g., spouse, relative, friend, or caregiver) during the interview. The study neurologist (J.G.G.) reviewed all questionnaires in their presence to resolve any ambiguities and determine final scores.

Briefly, the ESS is an 8-item questionnaire that measures one’s chances of “dozing off” in different daytime situations over the past week; scores range from 0 to 24 with scores $\geq$10 indicating excessive daytime sleepiness [13]. The PSQI assesses sleep quality over the past month; 19 individual items generate 7 component scores, which are summed for a global score, ranging from 0 to 21 and with scores $>$ 5 indicating poor sleep [14]. Presence or absence of probable RBD (pRBD) was examined with the question: “does the subject appear to act out his/her dreams while sleeping [e.g., push or flail their arms, shout, or scream]?” from the National Alzheimer’s Coordinating Center Uniform Data Set [16]. Motor symptoms were examined in the “on” state using the MDS-Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) Part III motor score and Hoehn and Yahr stage [17]. Medications taken by patients for PD, sleep, mood, and cognition were recorded. PD medications were converted to levodopa equivalent daily doses (LEDD) [18].

The neuropsychological evaluation included: 1) cognitive and mood assessments, 2) a semi-structured interview with the patient and/or informant, and 3) clinical impressions of the patient’s general cognitive function and functional abilities. Cognitive assessments included the Folstein Mini-Mental State Examination (MMSE) and the following individual tests grouped into 5 cognitive domains: (a) attention and working memory (Digit span backwards and Letter Number Sequencing from the Weschler Adult Intelligence Scale-III [WAIS-III], Trail making Test-A), (b) executive function (animal naming in 1 min, Controlled Oral Word Association Test, and Goodglass and Kaplan Clock Drawing Test), (c) language (Boston Naming Test, WAIS-III Similarities), (d) memory (3 trials of word list learning and delayed recall from the Consortium to Establish a Registry for AD [CERAD], Logical Memory I and II prose passages), and (e) visuospatial function (Benton Judgment of Line Orientation, Goodglass and Kaplan Clock Copying Test). The Hamilton Depression Rating Scale was used to assess depression.

2.3. Cognitive classification

PD patients were classified into cognitive groups (PD-NC, PD-MCI, PDD) in a consensus conference (neurologist, J.G.G.; neuropsychologists, G.T.S. and B.B.), using semi-structured interviews with the patient and/or informant, clinical and neuropsychological data and MDS diagnostic criteria for both PD-MCI (Level II, comprehensive assessment) [9] and PDD [19]. Raw scores for cognitive tests were transformed to *z*-scores based upon normative data from healthy, cognitively normal controls at our center [20]. Impairment on neuropsychological tests was demonstrated by z-scores of ≤ -1.5 on at least two neuropsychological tests (either two impaired tests in one cognitive domain or one impaired test in two different cognitive domains) [9]. Cognitive domain scores were calculated by averaging *z*-scores for neuropsychological tests within specific domains.

2.4. Statistical analysis

Statistical analyses were performed using SAS 9.1 (Institute Inc., Cary, NC). Demographic and disease-related variables were compared across PD cognitive groups using one-way analysis of variance (ANOVA), Kruskal–Wallis, Chi-square, or Fisher’s Exact test, as appropriate. Analyses were adjusted for multiple comparisons using Bonferroni corrections. Relationships between sleep scales, cognitive measures, and medications were examined with Pearson or Spearman’s correlations or Wilcoxon rank-sum test, as appropriate. Multivariate analysis was performed with proportional odds model with odds ratios (OR), 95% confidence intervals (CI), and Nagelkerke pseudo *R*-square (R^2) reported. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Patient characteristics

Clinical and neuropsychological features of the cohort are presented in Table 1. There were no significant differences among the groups in age, gender, or education. Disease duration, however, significantly differed among the groups (F [2,90] = 10.1, $p = 0.0001$), with post-hoc comparisons revealing longer disease duration in PDD patients compared to PD-NC patients ($p = 0.001$). Motor severity differed significantly among the groups, measured by MDS-UPDRS Part III motor scores (F [2,90] = 9.9, $p < 0.0001$) and Hoehn and Yahr stage ($\chi^2 = 26.7$, $p < 0.0001$). PDD patients had

Table 1
Demographic and clinical characteristics of our PD cohort.

	PD-NC, $n = 28$	PD-MCI, $n = 40$	PDD, $n = 25$	p value
Demographics				
Age, *y*	72.1 ± 6.1	73.5 ± 6.2	75.5 ± 6.8	0.15
Male, *n* (%)	20 (71.4)	32 (80)	17 (68)	0.52
Education, *y*	15.6 ± 2.8	14.8 ± 3.5	15.2 ± 3.0	0.64
PD duration, *y*	8.9 ± 3.0	10.1 ± 4.3	13.8 ± 5.1	<0.0001*
Motor and non-motor features				
MDS-UPDRS motor score	31.3 ± 8.4	37.3 ± 12.1	45.5 ± 13.9	<0.0001*
Hoehn and Yahr stage, median (range)	2.0 (2–3)	2.0 (2–5)	3.0 (2–5)	<0.0001*
Probable RBD, *n* (%)	15 (53.6)	25 (62.5)	11 (44)	0.34
Medications				
LEDD, mg/d	683.9 ± 387.7	856.6 ± 415.4	831.9 ± 306	0.17
Dopamine agonist, *n* (%)	14 (50.0)	17 (42.5)	4 (16)	0.03+
Amantadine, *n* (%)	3 (10.7)	10 (25)	1 (4)	0.05
Selegiline, *n* (%)	1 (3.6)	5 (12.5)	2 (8)	0.43
Sleep medication, *n* (%)	6 (21.4)	13 (32.5)	8 (32)	0.57
Antidepressant, *n* (%)	4 (14.3)	11 (27.5)	4 (16)	0.34
Cognitive enhancing medication, *n* (%)	1 (3.6)	5 (12.5)	13 (52)	<0.0001*
Cognitive and neuropsychological features				
Attention/working memory domain	−0.34 (0.51)	−1.41 (0.84)	−2.87 (1.63)	<0.0001^
Executive function domain	−0.23 (67)	−1.57 (0.82)	−2.89 (0.90)	<0.0001^
Language domain	0.11 (0.56)	−0.71 (0.80)	−1.92 (1.32)	<0.0001^
Memory domain	−0.34 (0.69)	−1.14 (0.79)	−3.11 (1.17)	<0.0001^
Visuospatial domain	−0.11 (0.82)	−1.45 (1.32)	−3.53 (2.01)	<0.0001^
MMSE scores	28.6 ± 1.1	27.6 ± 1.7	20.1 ± 6.2	<0.0001^
Hamilton depression rating scale	5.1 ± 3.1	6.1 ± 3.9	7.6 ± 3.9	0.06

Results are expressed as mean ± SD, unless otherwise noted.
Abbreviations: LEDD = levodopa equivalent daily doses, MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale, MMSE = Mini-Mental State Examination, RBD = REM behavior disorder.
* Comparisons between PD-NC vs. PDD and PD-MCI vs. PDD; + comparisons between PD-NC vs. PDD; ^comparisons between PD-NC vs. PD-MCI, PD-NC vs. PDD and PD-MCI vs. PDD.

worse motor scores compared to PD-NC ($p = 0.0001$) and PD-MCI ($p = 0.02$) patients and more advanced Hoehn and Yahr stages compared to PD-NC ($p = 0.0001$) and PD-MCI ($p = 0.0003$). There were no significant differences among the groups regarding daily levodopa equivalent doses. PD-NC patients, however, were more frequently treated with dopamine agonists, compared to PDD patients ($p = 0.03$). There were no significant differences among the groups for selegiline use, but there was a trend for greater amantadine use in PD-MCI patients, compared to PDD patients ($p = 0.05$). No significant differences among the groups were seen regarding medications used for sleep or mood. Of the 27 patients taking medications for sleep disturbances, 7 received benzodiazepines (2 PD-NC, 4 PD-MCI, 1 PDD patient); the remaining 20 used melatonin, mirtazapine, quetiapine, trazadone or zolpidem. Presence of pRBD symptoms was reported in 55% of our PD cohort, but did not differ significantly among cognitive groups ($\chi^2 = 2.15$, $p = 0.34$).

There were significant differences on raw neuropsychological scores and cognitive domain *z*-scores among the cognitive groups ($p < 0.0001$, all comparisons). Consistent with our cognitive group definitions, cognitive performance was worst in PDD patients and best in PD-NC patients (Supplemental Table). There were significant differences among the groups in their use of cognitive-enhancing medications (i.e., cholinesterase inhibitors, memantine) ($p < 0.001$), with PDD patients more frequently receiving these medications compared to PD-NC ($p < 0.0001$) and PD-MCI ($p = 0.001$) patients. PD patients had low Hamilton depression rating scale scores (mean 6.2 ± 3.8), thereby indicating a non-depressed cohort.

3.2. Sleep scales in the PD cohort

The PD cohort exhibited daytime and nighttime sleep dysfunction, with mean ESS scores of 9.4 ± 5.0 and mean PSQI scores, 6.7 ± 3.1. Additionally, 49.5% had ESS scores ≥10, a cut-off signifying excessive daytime sleepiness [13], and 59.1% had PSQI scores > 5, a cut-off designating poor nighttime sleep quality [14]. All combinations of clinically pertinent sleep-wake problems were represented: poor nighttime sleep with ($n = 33$) or without excessive daytime sleepiness ($n = 22$) and good nighttime sleep with ($n = 13$) or without excessive daytime sleepiness ($n = 25$). Overall, daytime and nighttime sleep abnormalities were not strongly associated with each other, with ESS and PSQI scores demonstrating modest, although statistically significant, correlations ($r = 0.22$, $p = 0.03$). Neither ESS nor PSQI scores correlated significantly with use of dopamine agonists ($p = 0.41$, $p = 0.77$, respectively), levodopa doses ($p = 0.16$, $p = 0.09$, respectively), or LEDD ($p = 0.55$, $p = 0.34$, respectively).

3.3. Relationships of the sleep scales to cognitive group

The two sleep scales differed in their relationship to PD cognitive status on univariate analyses (Table 2, Fig. 1). Mean ESS scores differed significantly among the groups ($F[2,90] = 5.67$, $p = 0.005$) with PDD patients having greater daytime sleepiness than PD-NC and PD-MCI patients ($p = 0.006$ and $p = 0.02$, respectively). ESS scores ≥10 occurred in 76% of PDD patients compared to 32.1% of PD-NC and 45% of PD-MCI patients ($\chi^2 = 10.72$, $p = 0.005$). In

Table 2
Sleep scale results for the PD cognitive groups.

	PD-NC, $n = 28$	PD-MCI, $n = 40$	PDD, $n = 25$	p value
ESS	7.9 ± 3.7	8.8 ± 5.3	12.1 ± 5.0	0.005*
ESS ≥10, *n* (%)	9 (32.1)	18 (45.0)	19 (76.0)	0.005*
PSQI	6.2 ± 2.8	7.0 ± 3.2	7.0 ± 3.3	0.60
PSQI > 5, *n* (%)	15 (53.6)	24 (60.0)	16 (64)	0.74

Results are expressed as mean ± SD, unless otherwise noted.
Abbreviations: ESS = Epworth Sleepiness Scale, PSQI = Pittsburgh Sleep Quality Index.
* Comparisons between PD-NC vs. PDD and PD-MCI vs. PDD.

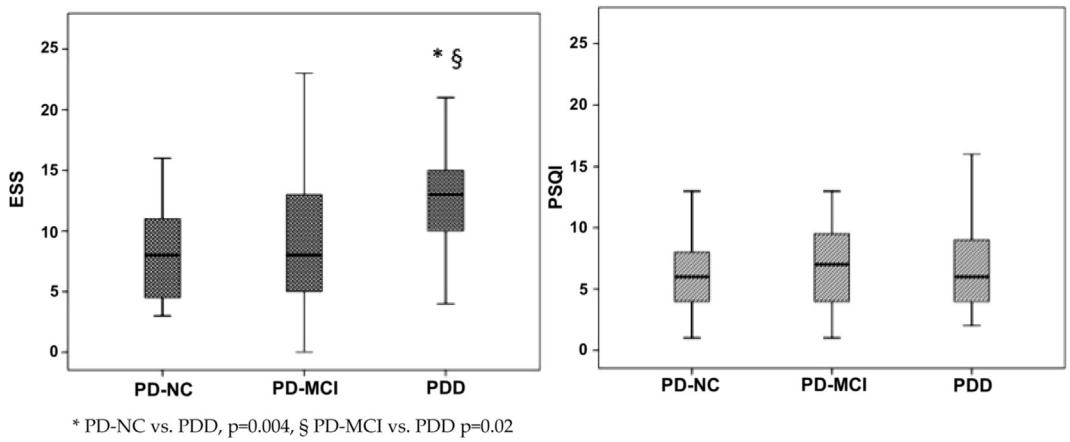

Fig. 1. Sleep scales across the PD cognitive groups. Boxplots depicting median and inter-quartile ranges for the ESS and PSQI scales across the cognitive groups. * PD-NC vs. PDD, $p = 0.004$, § PD-MCI vs. PDD $p = 0.02$.

contrast, mean PSQI scores did not differ significantly among the groups (F [2,90] = 0.52, $p = 0.60$). PSQI scores > 5 were frequent in all cognitive groups, occurring in 53.6% of PD-NC, 60% of PD-MCI, and 64% of PDD patients ($\chi^2 = 0.61$, $p = 0.74$).

Table 3 depicts the multivariate analyses of the relationship between ESS and PSQI, examined as both continuous measures and binary measures, and PD cognitive status, adjusting for age, PD duration, LEDD, Hoehn and Yahr stage, and presence/absence of reported pRBD, in each model. Analyses with the sleep scales as continuous measures revealed a significant association with Hoehn and Yahr (OR = 3.24, CI = [1.54, 6.81], $p = 0.002$) but not with age ($p = 0.06$), PD duration ($p = 0.06$), LEDD ($p = 0.57$), pRBD ($p = 0.51$), or the ESS and PSQI scales ($p = 0.4$, $p = 0.9$, respectively). With ESS and PSQI scores as binary measures, as defined above, there was a significant association with Hoehn and Yahr (OR = 3.16, CI = [1.51, 6.6], $p = 0.002$) and mildly, but significantly, with age (OR = 1.08, CI = [1, 1.16], $p = 0.04$), but not with PD duration ($p = 0.06$), LEDD ($p = 0.5$), pRBD ($p = 0.65$), or the ESS and PSQI scales ($p = 0.19$, $p = 0.56$, respectively). Of the variables, worse motor severity was most strongly related to worse PD cognitive status.

Table 3
Multivariate analyses of the sleep scales and PD cognitive groups.

Variable	OR	95% CI	p value
A. ESS and PSQI as continuous measures			
ESS	1.04	0.94–1.15	0.4
PSQI	1.0	0.87–1.15	0.97
Age	1.07	0.99–1.15	0.06
PD duration	1.11	0.99–1.25	0.06
Hoehn and Yahr stage	3.24	1.54–6.81	0.002
Probable RBD	1.34	0.57–3.16	0.51
LEDD	1.03	0.92–1.17	0.57
B. ESS and PSQI as binary measures			
ESS ≥10 vs. <10	1.91	0.72–5.08	0.19
PSQI >5 vs. ≤5	0.78	0.33–1.84	0.56
Age	1.08	1–1.16	0.04
PD duration	1.11	0.99–1.24	0.06
Hoehn and Yahr stage	3.16	1.51–6.6	0.002
Probable RBD	1.22	0.51–2.91	0.65
LEDD	1.04	0.92–1.17	0.5

A. Nagelkerke R-square = 0.38.
B. Nagelkerke R-square = 0.39.
Abbreviations: CI = confidence interval, ESS = Epworth Sleepiness Scale, LEDD = levodopa equivalent daily doses, OR = Odds ratio, PSQI = Pittsburgh Sleep Quality, RBD = REM behavior disorder.

3.4. Sleep scales and cognitive domains

The ESS and PSQI scales exhibited divergent relationships with measures of global and domain-specific cognitive function. ESS scores correlated with MMSE scores ($r = -0.31$, $p = 0.002$), whereas PSQI scores did not ($r = -0.018$, $p = 0.87$). Moreover, ESS scores correlated with impairments in cognitive domains of attention and working memory ($r = -0.38$, $p < 0.0001$), executive function ($r = -0.34$, $p = 0.001$), memory ($r = -0.31$, $p = 0.003$), and visuospatial abilities ($r = -0.35$, $p = 0.001$); ESS scores did not correlate significantly with the language domain. PSQI scores, however, did not correlate with any cognitive domain scores: attention and working memory ($r = -0.07$, $p = 0.53$), executive function ($r = 0.03$, $p = 0.78$), language ($r = -0.06$, $p = 0.58$), memory ($r = -0.13$, $p = 0.21$), and visuospatial abilities ($r = -0.004$, $p = 0.97$).

4. Discussion

Our study demonstrates that daytime sleepiness in PD, but not nighttime sleep quality, as measured by the ESS and PSQI, respectively, is associated with cognitive impairment in PD and worse performance in cognitive domains of attention/working memory, executive function, memory, and visuospatial function. To our knowledge, our study is the first to examine the interdependence of self-reported daytime and nighttime sleep disturbances across the full PD cognitive spectrum, spanning normal cognition to mild cognitive impairment to dementia, and in particular, regarding specific cognitive domain deficits.

PDD patients had significantly higher ESS scores reflecting daytime sleepiness, compared to both PD-NC and PD-MCI patients, despite similar nighttime sleep reports. The finding of higher ESS scores in the PDD group extends other reports of close associations between daytime sleepiness and dementia syndromes, including Alzheimer's disease, vascular dementia, and DLB patients [21–23] and in a large population-based study of older adults, in which excessive daytime sleepiness, but not insomnia or other nighttime sleep complaints, was significantly worse in the demented group [22]. In our PD cohort, we also found that 45% of the PD-MCI patients had ESS scores ≥10, despite similar PSQI scores as the PD-NC and PDD groups. Mean ESS scores for the PD-MCI group fell between scores of the PD-NC and PDD groups, ranging from 0 to 23 (maximum 24); the wide range of ESS scores in our PD-MCI group may reflect the underlying heterogeneity in severity and phenotype of cognitive deficits in PD-MCI. Longitudinal follow-up of our PD-MCI patients, particularly those with higher baseline ESS scores,

will help clarify the relationships of sleep-wake disturbances to specific PD-MCI subtypes and effects of daytime sleepiness on conversion to PD dementia.

One prior study investigated the relationship of daytime and nighttime sleep disturbances and neuropsychological functions in PD but included only non-demented PD patients and focused on individual neuropsychological tests [24]. Modest, but significant, relationships between the day and night subsections of the Scales for Outcomes in PD-Sleep Scale (SCOPA) and the ESS and several individual neuropsychological tests emerged. Worse ESS scores were associated with poorer performance on Trail Making Test B-A analyses and choice reaction time tasks, though there was no relationship between SCOPA-day scores and cognitive performance; worse SCOPA-night scores were associated with greater impairment on Digit Span backwards and Logical Memory tests. Our study demonstrated similar associations between excessive daytime sleepiness and deficits in attention/working memory and executive function, but in contrast to this study [24], we did not find significant correlations between nighttime sleep quality and any cognitive measure. One other study reported that ESS scores did not correlate significantly with attention/executive function, memory, and psychomotor function, but the primary emphasis of this study was on nighttime function with actigraphy in non-demented PD patients; furthermore, no details of the ESS scores or their relationships were provided [25]. Several key methodological differences between these studies and ours could account for differences in results, including differences in sleep and cognitive measures (i.e., scales used, comparison of cognitive domains or individual neuropsychological tests) and PD patient population (i.e., treated patients, inclusion of demented patients). Nonetheless, sleep-wake disturbances may relate differently to specific elements of PD cognition, and further study of these relationships may advance our understanding of their underlying neural substrates and development of therapeutic interventions for both sleep and cognition.

Our findings of abnormal ESS scores with or without poor PSQI scores reinforce that excessive daytime sleepiness is not just a secondary consequence of poor nighttime sleep or other features such as dopaminergic medications. Non-demented PD patients may exhibit an increased drive to sleep or excessive daytime sleepiness, using multiple sleep latency tests or ESS scores, without any significant changes in polysomnographic measures of sleep efficiency, total sleep time, or REM sleep [3,4,26]. Thus, impaired wakefulness in PD may reflect neuronal loss and Lewy body accumulation in the brainstem, basal forebrain regions, hypothalamus, and thalamus and accompanying neurochemical alterations in cholinergic, monoaminergic, dopaminergic, and histaminergic systems or the modulatory orexin/hypocretin systems [27]. Of note, similar neuroanatomical regions and neurotransmitter systems to those involved in sleep-wake regulation are implicated in attention, executive function, learning, and memory [19,27]. In our cohort, dopaminergic medications did not account for the greater daytime sleepiness in cognitively impaired PD patients. While dopamine agonists may be associated with excessive daytime sleepiness [28], they were used less frequently by PDD patients, who represented the sleepiest group with higher ESS scores compared to PD-NC and PD-MCI patients. In addition, levodopa doses, which have been associated with sleepiness in some studies, did not differ significantly among our cognitive groups [29,30]. Our data, however, cannot separate the effect of worse motor severity, as measured by Hoehn and Yahr stage, on excessive daytime sleepiness and cognitive status. This may relate, in part, to underlying interactions between daytime sleepiness and features of advanced PD, including both increased motor severity and greater cognitive dysfunction. Additional studies including larger PD cohorts and also representing broader distributions of ages, PD durations, and motor stages may help elucidate the relationship of sleep-wake disturbances to these features and avoid Type 2 errors that can occur with small sample sizes.

Strengths of our study include a large, well-defined PD cohort, PD diagnoses by Movement Disorder specialists, uniform data collection with informant corroboration in all PD cases regardless of cognitive status, and detailed cognitive and motor evaluations. In addition, we used validated subjective sleep scales that have been recommended by the MDS for use in PD and incorporated recently recommended diagnostic criteria for PD-MCI and PDD. As the aim of our study was to examine the ESS and PSQI scales and to focus on patient/caregiver perceptions of sleep aberrations, we did not include formal, objective sleep and wakefulness tests (e.g., polysomnograms or multiple sleep latency tests) as screening or outcome measures. Extension of our study to include these types of measures is an opportunity for future study. We acknowledge limitations including that the informants, although they accompanied all PD patients, regardless of cognitive status, and knew them well, did not always include a bed partner; the presence/absence of pRBD symptoms was ascertained using a single-item question, though this approach has been recently utilized [31]; and our university setting may limit generalizability to community populations. Future studies may evaluate other features related to sleep or wakefulness including specific questionnaires for co-morbid sleep disorders (e.g., obstructive sleep apnea, restless legs syndrome, periodic limb movements) or consumption of caffeine-containing products.

We conclude that excessive daytime sleepiness is associated with PD cognitive impairment, independent of nighttime sleep disturbances, as measured by the ESS and PSQI, respectively. Future studies will be necessary to determine the long-term cognitive consequences of daytime sleepiness in PD, examine if these sleep disturbances predict conversion of PD-NC to PD-MCI and PDD, and understand the relationships among sleep, cognitive, and motor dysfunction.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2013.05.006.

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